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SEARCH FOR NEW DRUGS

HEMOCOAGULATION ACTIVITY OF SULFUR-CONTAINING PINANE-TYPE TERPENOIDS

S. V. Kiselev,[1] L. E. Nikitina,[1] V. A. Startseva,[1] N. P. Artemova,[1] A. V. Bodrov,[1] S. V. Boichuk,[1] M. M. Vorontsova,[2] A. A. Rakhmatullina,[2] R. G. Turaev,[2] and V. V. Klochkov[3]

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A series of pinane-type sulfides and sulfoxides were synthesized from (1*S*)-(–)-β-pinene. Their hemocoagulation activity *in vitro* on human blood plasma was studied. All tested compounds exhibited antiaggregation and anticoagulation activity. The most water-soluble sulfoxide with a mercaptoacetic acid moiety inhibited spontaneous platelet aggregation and that induced by collagen and arachidonic acid and also reduced the coagulation activity of human blood plasma. The hemocoagulation activity was due to selective inhibition of platelet receptors, decreased yield of thrombocytic microvesicles, and suppression of their activity.

Keywords: (1*S*)-(–)-β-pinene, sulfides and sulfoxides, platelets, antiaggregation and anticoagulation activity.

Cardiovascular diseases, among which ischemic heart disease (IHD) (51%) and ischemic infarct (27%) play leading roles, remain the main global cause of death. These diseases result from atherosclerotic inflammation of the blood vessels that damages the vessel wall and activates platelets and coagulation hemostasis, which in turn causes clots to form and blood flow to vitally important organs to stop. These changes are induced by various physiological and pathological agents that activate specific cellular receptors that transform the cellular membrane and render its surface thrombogenic. The search for new drugs capable of affecting these processes and correcting them is a critical task for designing anticlotting drugs. We hypothesized that sulfur(S)-containing terpenoids may possess such properties.

We showed earlier that S-containing monoterpenoids synthesized by us possessed high antifungal, anti-inflammatory, and antihelicobacter activity in combination with low toxicity [1 – 3].

[1] Kazan State Medical University, Kazan, Tatarstan, 420012 Russia; e-mail: nikitl@mail.ru.
[2] Republican Hematology Center, Kazan, Tatarstan, 420140 Russia; e-mail: rspk@tatar.ru.
[3] Kazan (Volga Region) Federal University, Kazan, Tatarstan, 420008 Russia; e-mail: vladimir.klochkov@kpfu.ru.

Herein, pinane-type sulfides **II** and **III** and sulfoxides **IV** – **VI** were investigated for the first time for possible application to correct disruptions of an *in vitro* hemostasis system. The sulfides were synthesized by electrophilic addition of thiols to the double bond of (1*S*)-(–)-β-pinene (**I**) in the presence of $ZnCl_2$ [4]. Sulfoxides **IV** and **V** were prepared via oxidation of the corresponding sulfides using *m*-chloroperbenzoic acid [5 – 7]; sulfoxide **VI**, using peracetic acid.

The structures of the products isolated by column chromatography were established using spectral data.

EXPERIMENTAL CHEMICAL PART

PMR spectra were measured in $CDCl_3$ with TMS internal standard on a Varian Unity spectrometer (300 MHz). Reaction products were isolated and purified using adsorption chromatography over silica gel L (100/160). The course of reactions and separation efficiency of reaction mixtures were monitored by TLC on Silufol plates (I_2 detection). The syntheses and spectral data of **I** – **V** were published before [3, 4]. Solvents were purified and dried using known methods [8].